REMARKS

I. Amendments

A. Claims

Claims 8, 10 and 17-22 have been canceled. Claims 24-29 have been added. The newly added claims do not add or constitute new matter, and are completely supported by the application as originally filed. Support may be found throughout the specification and in the originally filed claims. Specifically, support for the transgenic mice recited in claims 24-27 and 29 may be found, for example, in original claims 18-22 and at page 53, line 13 through page 54, line 10, of the specification. Support for the method of producing the transgenic mouse recited in claim 28 may be found, for example, at page 11, line 19 through page 18, line 4, and at page 53 lines 16-29, of the specification.

The amendments to the claims are made without prejudice to the pending or now-canceled claims or to any subject matter pursued in related applications. Moreover, the amendments are made solely to expedite prosecution of the application and are not intended to limit the scope of the invention. The Applicant reserves the right to prosecute any canceled subject matter at a later time or in a later filed divisional, continuation or continuation-in-part application.

B. Specification

The amendment to the specification at the Brief Description of the Drawings has been made to address the Examiner's objection with respect to Figure 2A. No new matter has been added by this amendment. Support for this amendment may be found, for example, in Figure 2A as originally filed, and at page 53, lines 18-22 of the specification.

C. Drawings

New Figure 2A has been submitted to provide a sequence identifier fo the sequence described in Figure 2A, for which sequence identifier was inadvertently omitted in Figure 2A as originally filed. The Applicant has requested substitution of new Figure 2A for originally filed Figure 2A, and has enclosed both a marked-up version, with corrections indicated in red ink, and a clean version including the corrections. New Figure 2A does not constitute new matter and is supported by the application as filed.

Upon entry of the foregoing amendments, claims 24-29 are pending in the instant application.

II. Formalities

The Examiner has noted that an information disclosure statement, in addition to that submitted on October 29, 2001, may have been submitted on or around November 28, 2001, which has not been found, and thus could not be considered by the Examiner. Applicant thanks the Examiner, but believes that the information disclosure statement filed October 29, 2001 is the only one filed in this case as of this time.

III. Objections

The Examiner has objected to the Brief Description of the Drawings in the instant specification because there is no description of Figure 2A. The Applicant disagrees in that Figure 2A has been adequately described at page 11, line 5. However, the Applicant has amended the Brief Description of the Drawings to address the Examiner's objection.

Further, the Examiner has objected to the sequence disclosed in Figure 2A as being an unidentified sequence, and thus not complying with the requirements of 37 CFR 1.821-1.825. The Applicant has submitted a new Figure 2A for approval by the Examiner, which figure includes a sequence identifier for the sequence disclosed therein.

IV. Rejections

A. Rejections under 35 U.S.C. § 112, first paragraph

1. Enablement

Claims 8, 10 and 17-22 were rejected under 35 U.S.C. § 112, first paragraph, because, according to the Examiner, the specification does not enable any person skilled in the art to which it pertains to make and use the invention commensurate in scope with the claims. The Applicant respectfully traverses this rejection. However, in view of the cancellation of claims 8, 10 and 17-22, the Examiner's rejection under 35 U.S.C. § 112, first paragraph, is no longer relevant.

Specifically, in the rejection, the Examiner asserts that due to the nature of the invention, the breadth of the claims, and the state of the art of transgenic knockout technology, the specification does not provide an enabling disclosure for all of the transgenic non-human animals embraced by the claims. More particularly, according to the Examiner, while the specification

has taught the generation of a transgenic mouse having the phenotype of decreased activity, hypoactivity or decreased susceptibility to seizure, the specification has not taught the generation of the other transgenic non-human animals encompassed by the claims. Further, the Examiner asserts that although the specification has taught a method of producing the transgenic mouse, which requires introduction of a targeting construct into an embryonic stem cell, it has not taught how to create the transgenic mouse by a method wherein the targeting construct is introduced into any other cell. The Examiner further asserts that although the specification has provided guidance for the transgenic mouse comprising a disruption in a CRFR2 gene comprising SEQ ID NO:1, it has not provided any teachings with regard to homologs of this sequence, which homologs are encompassed by the original claims.

The Applicant respectfully disagrees with the Examiner's conclusions. However, claims 8, 10 and 17-22 have been cancelled. The Applicant submits that the specification provides sufficient enabling disclosure for the transgenic mice and methods of producing the transgenic mice as currently recited in new claims 24-29. More particularly, the scope of the current claims, which encompass a transgenic mouse whose genome comprises a homozygous disruption in an endogenous CRFR2 gene, where the disruption leads to a phenotype of decreased activity or decreased susceptibility to seizure, is sufficiently enabled by the disclosure of the instant specification.

As this rejection under 35 U.S.C. § 112, first paragraph, of claims 8, 10 and 17-22 is no longer relevant as a result of the cancellation of these claims, and new claims 24-29 are fully enabled by the teachings of the specification as noted above, Applicant respectfully requests withdrawal of this rejection under 35 U.S.C. § 112, first paragraph.

2. Written Description

Claims 17-22 were further rejected by the Examiner under 35 U.S.C. § 112, first paragraph, as containing subject matter not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor had possession of the invention at the time of filing of the instant application. The Applicant respectfully traverses this rejection under 35 U.S.C. § 112, first paragraph, in light of the cancellation of claims and the arguments presented below.

Specifically, the Examiner asserts that although the specification has provided a description for the nucleotide sequence set forth in SEQ ID NO:1, which encodes a CRFR2, it

has not disclosed the nucleotide sequences of any nucleic acids that are homologs of the nucleotide sequence set forth in SEQ ID NO:1. Further, the Examiner states that there is no evidence of record or in the art that shows a structural relationship between the disclosed sequences and homologs thereof, nor any indication that their biological activity would be similar. The Applicant respectfully disagrees with the Examiner's conclusions in that the inventor or other person skilled in the art would be aware of homologs of the sequence set forth in SEQ ID NO:1. However, as claims 17-22 have been cancelled, and new claims 24-29 no longer recite homologs of SEQ ID NO:1, the rejection is moot.

The Applicant submits that new claims 24-29 have sufficient written description support in the instant application. These claims relate to disruptions in an endogenous CRFR2 gene in a transgenic mouse, which have been described and defined adequately in the instant specification. More particularly, the claims encompass transgenic mice that exhibit a phenotype of decreased activity or decreased susceptibility to seizure, as a result of such a disruption in an endogenous CRFR2 gene. The generation of such a transgenic mouse has been sufficiently described in the specification, and in particular, in the working example provided on pages 53-54.

As claims 17-22 have been cancelled, and the originally filed specification adequately demonstrates possession of the invention recited in new claims 24-29 as required by 35 U.S.C. § 112, the written description rejection under 35 U.S.C. § 112, first paragraph, is no longer relevant. The Applicant respectfully requests withdrawal of this rejection.

B. Rejections under 35 U.S.C. § 102

Claims 8 and 10 were rejected under 35 U.S.C. § 102 as being anticipated by Coste *et al.*, 2000, *Nature Genetics,* 24:403-409 ("Coste"). The Applicant respectfully traverses this rejection. However, in view of the cancellation of claims 8 and 10, the rejection under 35 U.S.C. § 102 is no longer relevant.

Specifically, according to the Examiner, the teachings of Coste anticipate all of the instant claim limitations. More particularly, the Examiner asserts that Coste discloses a transgenic mouse comprising a disruption in the CRHR2 (interpreted to be CRFR2) gene, which is created by introducing a targeting vector into ES cells, transferring the ES cells to a blastocyst and then implanting the blastocyst into a pseudopregnant female mouse, wherein said female mouse gives birth to a chimeric mouse, and breeding said chimeric mouse to produce the transgenic mouse.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. See MPEP § 2131. As Coste does not teach all of the claim limitations as recited, new claims 24-29 are not anticipated by this reference. The current claims encompass a transgenic mouse whose genome comprises a disruption in an endogenous CRFR2 gene, wherein the transgenic mouse exhibits decreased activity or decreased susceptibility to seizure, and a method of producing said transgenic mouse. Coste is limited to disclosing an example of the production of a mouse comprising a disrupted CRFR2. Coste fails to teach or even suggest the phenotype of the transgenic mouse of decreased activity or decreased susceptibility to seizure, as is recited in the current claims.

Claims 8 and 10 were further rejected under 35 U.S.C. § 102 as being anticipated by Bale *et al.*, 2000, *Nature Genetics,* 24:410-414 ("Bale"). The Applicant respectfully traverses this rejection. However, in light of the cancellation of claims 8 and 10, the rejection is no longer relevant.

According to the Examiner, Bale discloses a transgenic mouse comprising a disruption in the CRHR2 gene, which is created by introducing a targeting vector into ES cells, transferring the ES cells to a blastocyst and then implanting the blastocyst into a pseudopregnant female mouse, wherein said female mouse gives birth to a chimeric mouse, and breeding said chimeric mouse to produce the transgenic mouse. The Examiner asserts that Bale anticipates all of the instant claim limitations.

The disclosure of Bale generally relates to the role of CRHR2 in stress and anxiety-like behavior. More particularly, Bale is limited to disclosing an example of the production of a mouse comprising a disrupted CRHR2. Bale fails to disclose the phenotype of the transgenic mouse of the instant invention as presently claimed of decreased activity, hypoactivity or decreased susceptibility to seizure.

The Examiner has also rejected claims 8 and 10 under 35 U.S.C. § 102 as being anticipated by Kishimoto *et al.*, 2000, *Nature Genetics,* 24:415-419 ("Kishimoto"). The Applicant respectfully traverses this rejection. However, in light of the cancellation of claims 8 and 10, the rejection is no longer relevant.

Specifically, the Examiner states that Kishimoto discloses a transgenic mouse comprising a disruption in the CRHR2 gene, which mouse is created by introducing a targeting vector into ES cells, transferring the ES cells to a blastocyst and then implanting the blastocyst into a

pseudopregnant female mouse, wherein said female mouse gives birth to a chimeric mouse, and breeding said chimeric mouse to produce the transgenic mouse. The Examiner states that the teachings of Kishimoto anticipate all of the instant claim limitations.

The disclosure of Kishimoto generally relates to a putative anxiolytic role for CRHR2, particularly in male transgenic mice. Kishimoto discloses how to create a transgenic mouse comprising a disruption in CRHR2 which exhibits enhanced anxious behavior. Kishimoto fails to disclose or describe a transgenic mouse comprising a disruption in a CRFR2 gene which exhibits decreased activity or decreased susceptibility to seizure, as is presently recited in claims 24-29. As such, Kishimoto fails to teach or describe every claim limitation.

Finally, the Examiner has rejected claims 8 and 10 under 35 U.S.C. § 102 as being anticipated by Lee *et al.,* U.S. Serial No. 6,353,152, effective filing date July 15, 1999 ("Lee"). The Applicant respectfully traverses this rejection. However, in light of the cancellation of claims 8 and 10, the rejection is no longer relevant.

Specifically, the Examiner states that Lee discloses a transgenic mouse comprising a disruption in the CRFR2 gene, which mouse is created by introducing a targeting vector into ES cells, transferring the ES cells to a blastocyst and then implanting the blastocyst into a pseudopregnant female mouse, wherein said female mouse gives birth to a chimeric mouse, and breeding said chimeric mouse to produce the transgenic mouse. The Examiner states that the disclosure of Lee anticipates all of the instant claim limitations.

As the presently claimed invention, recited in claims 24-29, relates to a transgenic mouse whose genome comprises a disruption in an endogenous CRFR2 gene, wherein the transgenic mouse exhibits decreased activityor decreased susceptibility to seizure, and a method of producing the transgenic mouse, the Applicant does not agree that Lee anticipates all of the claimed limitations. Lee merely discloses a method of producing a transgenic mouse comprising a disruption in a CRFR2 gene, and analysis of these mice, for example, in tests for anxiety, stress and blood pressure. Specifically, Lee claims the transgenic mice comprising disruptions in CRFR2 genes and methods of using the transgenic mice. However, Lee fails to disclose the transgenic mice as presently claimed by the Applicant. In particular, Lee fails to disclose a transgenic mouse whose genome comprises a disruption in a CRFR2 gene, wherein the transgenic mouse exhibits decreased activity or decreased susceptibility to seizure, or methods of producing said transgenic mouse. Thus, Lee fails to teach all of the claimed limitations.

As the Applicant has cancelled claims 8 and 10, and new claims 24-29 are not anticipated by the teachings of Coste, Bale, Kishimoto or Lee for the reasons noted above, the rejections under 35 U.S.C. § 102 are no longer relevant. The Applicant requests withdrawal of the rejection under 35 U.S.C. § 102.

It is believed that the claims are in condition for allowance, and notice to that effect is respectfully requested. The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-1271 under Order No. R-616.

Respectfully submitted,

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Appendix A

(Marked up Version of Changes Made to Specification)

At the paragraph beginning at page 11, line 5

Figures 2A ~~-2B show~~ shows the design of the targeting construct used to disrupt CRFR2 genes (SEQ ID NO:1), including the location and extent of the disrupted portion of the CRFR2 gene, as well as the nucleotide sequences flanking the deleted portion. Figure 2B shows the sequences identified as SEQ ID NO:2 and SEQ ID NO:3, which were used as the 5'- and 3'-targeting arms (including the homologous sequences) in the CRFR2 targeting construct, respectively.

underlined = deleted in targeting construct

[ ] = sequence flanking Neo insert in targeting construct

GAATTCCGGGTGGGTAGGTCGGGCAGGGTAGGACAGGCCTAAGAGAGAGGCCGGACAGAC
CTCCTTTGGAAGCAGCCACTTCTGGTCCCCATCCCTGGAGCGATCGAGCGCAGGATCTGC
TGTCCCATGGGACAGCAGATCTCTCTTCCCAGTGCACAGCTTCTCCTCTGCCTGTTTTCC
CTGCTTCCAGTGCTCCAGGTGGCCCAACCAGGCCAGGCACCCCAGGACCAGCCCCTGTGG
ACACTTTTGGAGCAGTACTGCCACAGGACCACAATTGGGAATTTTTCAGGTCCCTACACC
TACTGCAACACGACCTTGGACCAGATCGGGACCTGCTGGCCACAGAGCGCACCCGGAGCC
CTAGTAGAGAGACCGTGCCCCGAGTACTTCAATGGCATCAAGTACAACACGACCC[GGAA
TGCCTACAGAGAGTGCCTGGA]GAACGGGACCTGGGCCTCAAGGGTCAACTACTCACACT
GCGAACCCATTTTGGATGACAAGCAGAGAAAGTATGACCTGCATTACCGAATCGCCCTCA
TTGTCAACTACCTGGGTCACTGTGTTTCCGTGGTGGCCCTGGTG[GCCGCTTTCCTGCTT
TTCCTAGTGCTGCG]GAGTATCCGCTGCCTGAGGAATGTGATCCACTGGAACCTCATCAC
CACCTTCATTCTGAGAAACATCGCGTGGTTCCTGCTGCAACTCATCGACCACGAAGTGCA
CGAGGGCAATGAGGTCTGGTGCCGCTGCATCACCACCATCTTCAACTATTTTGTGGTCAC
CAACTTCTTCTGGATGTTTGTGGAGGGCTGCTACCTGCACACGGCCATTGTCATGACGTA
CTCCACAGAGCACCTGCGCAAGTGGCTTTTCCTCTTCATTGGATGGTGCATTCCCTGCCC
TATCATCATCGCCTGGGCAGTTGGCAAACTCTACTATGAGAATGAGCAGTGCTGGTTTGG
CAAGGAAGCTGGTGATTTGGTGGACTACATCTACCAGGGCCCCGTCATGCTTGTGCTGTT
GATCAATTTTGTATTTCTGTTTAACATCGTCAGGATCCTGATGACGAAGTTACGAGCATC
CACCACGTCCGAGACAATCCAATACAGGAAGGCAGTGAAGGCCACGCTGGTCCTCCTCCC
CCTGTTGGGCATCACCTACATGCTCTTCTTTGTCAATCCTGGCGAGGACGACCTGTCCCA
GATTGTGTTCATCTACTTCAACTCTTTCCTGCAGTCCTTCCAGGGTTTCTTTGTGTCCGT
TTTCTACTGCTTCTTCAATGGAGAGGTGCGCGCGGCCCTGAGAAAGCGGTGGCACTCGGG
GCAGGACCACCACGCCCTCCGGGTGCCTGTGCGCCGGGCCATGTCCATCCCTACGTCGCC
CACCAGGATCAGCTTCCACAGCATCAAGCAGACAGCTGCTGTGTGACCCTCTGTCACCGT
CTGCCCGGCAGTCCACCACTGAGGCAGCTTCTCCATCCTTTACAGCCTTCCCCTGGGTCC
TCCTTGCTACCCTGACCCACAGGTACAAGGTACAGGAGAAGGGAGGAGAACGAACACTCC
C (SEQ ID NO.: 1)

FIGURE 2A

underlined = deleted in targeting construct

[ ] = sequence flanking Neo insert in targeting construct

GAATTCCGGGTGGGTAGGTCGGGCAGGGTAGGACAGGCCTAAGAGAGAGGCCGGACAGAC
CTCCTTTGGAAGCAGCCACTTCTGGTCCCCATCCCTGGAGCGATCGAGCGCAGGATCTGC
TGTCCCATGGGACAGCAGATCTCTCTTCCCAGTGCACAGCTTCTCCTCTGCCTGTTTTCC
CTGCTTCCAGTGCTCCAGGTGGCCCAACCAGGCCAGGCACCCCAGGACCAGCCCCTGTGG
ACACTTTTGGAGCAGTACTGCCACAGGACCACAATTGGGAATTTTTCAGGTCCCTACACC
TACTGCAACACGACCTTGGACCAGATCGGGACCTGCTGGCCACAGAGCGCACCCGGAGCC
CTAGTAGAGAGACCGTGCCCCGAGTACTTCAATGGCATCAAGTACAACACGACCC[GGAA
TGCCTACAGAGAGTGCCTGGA]GAACGGGACCTGGGCCTCAAGGGTCAACTACTCACACT
GCGAACCCATTTTGGATGACAAGCAGAGAAAGTATGACCTGCATTACCGAATCGCCCTCA
TTGTCAACTACCTGGGTCACTGTGTTTCCGTGGTGGCCCTGGTG[GCCGCTTTCCTGCTT
TTCCTAGTGCTGCG]GAGTATCCGCTGCCTGAGGAATGTGATCCACTGGAACCTCATCAC
CACCTTCATTCTGAGAAACATCGCGTGGTTCCTGCTGCAACTCATCGACCACGAAGTGCA
CGAGGGCAATGAGGTCTGGTGCCGCTGCATCACCACCATCTTCAACTATTTTGTGGTCAC
CAACTTCTTCTGGATGTTTGTGGAGGGCTGCTACCTGCACACGGCCATTGTCATGACGTA
CTCCACAGAGCACCTGCGCAAGTGGCTTTTCCTCTTCATTGGATGGTGCATTCCCTGCCC
TATCATCATCGCCTGGGCAGTTGGCAAACTCTACTATGAGAATGAGCAGTGCTGGTTTGG
CAAGGAAGCTGGTGATTTGGTGGACTACATCTACCAGGGCCCCGTCATGCTTGTGCTGTT
GATCAATTTTGTATTTCTGTTTAACATCGTCAGGATCCTGATGACGAAGTTACGAGCATC
CACCACGTCCGAGACAATCCAATACAGGAAGGCAGTGAAGGCCACGCTGGTCCTCCTCCC
CCTGTTGGGCATCACCTACATGCTCTTCTTTGTCAATCCTGGCGAGGACGACCTGTCCCA
GATTGTGTTCATCTACTTCAACTCTTTCCTGCAGTCCTTCCAGGGTTTCTTTGTGTCCGT
TTTCTACTGCTTCTTCAATGGAGAGGTGCGCGCGGCCCTGAGAAAGCGGTGGCACTCGGG
GCAGGACCACCACGCCCTCCGGGTGCCTGTGCGCCGGGCCATGTCCATCCCTACGTCGCC
CACCAGGATCAGCTTCCACAGCATCAAGCAGACAGCTGCTGTGTGACCCTCTGTCACCGT
CTGCCCGGCAGTCCACCACTGAGGCAGCTTCTCCATCCTTTACAGCCTTCCCCTGGGTCC
TCCTTGCTACCCTGACCCACAGGTACAAGGTACAGGAGAAGGGAGGAGAACGAACACTCC
C (SEQ ID NO:1)

FIGURE 2A